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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/399,120	09/20/1999	DESMOND MASCARENHAS	220952029300	1886

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EXAMINER	
GUPTA, ANISH	
ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 11/05/2002

17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/399,120	MASCARENHAS, DESMOND	
	Examiner	Art Unit	
	Anish Gupta	1653	

-- Th MAILING DATE of this communication app ars on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 August 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *11-15 and 17* is/are withdrawn from consideration.

5)☐ Claim(s) *1-10,16 and 18-44* is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The amendment filed, 8-28-02, is hereby acknowledged. The amendment amended claim 7-8 and 18-44 were added. Claims 1-44, are pending in the application.

2. Applicant's election without traverse of Group I, claims 1-10 and 16 in Paper No. 8 is acknowledged. Claims 11-15, 17 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group II, there being no allowable generic or linking claim. Election was made without traverse in Paper No. 8. Newly added claims, 18-44, have been placed in Group I and thus have been examined along with claims 1-10 and 16.

A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112
First Paragraph

4. Claims 1-10, 16 remain and newly added claims 18-44 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons set forth in the previous office action and the reasons set forth below.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400

(Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

Applicants argue that the specification provides ample guidance on how to use the claimed invention. Applicants state that the structure of new analogs can be predicted using computer modeling. Applicants have stated that the critical regions of IGFBP have been defined in the art and thus one "skilled in the art would be able to alter amino acid residues in the binding protein and/or receptor binding domain (which are distal to each other), without substantially changing the protein structure." Further, testing of the IGF analogs can be accomplished by using routine binding assays. Applicants assert that they are not required to demonstrate each species of null IGF is effective in inhibit growth rate of a tumor and the burden is on the Examiner to assert why other species of null IGF would not work in slowing tumor growth rate. "The specification provides a theoretical basis for the importance of two properties, i.e., null IGF displaces native IGF-1 from complexes with binding protein....resulting in reduced IGF-1 activity, which reduces growth of tumors." Further, Applicants state that the burden of providing basis for determining that null IGF, other than Y60L, will not work has not been met by the Examiner.

Applicant's arguments filed 8-21-02 have been fully considered but they are not persuasive.

Applicants argue that the burden of providing basis for concluding that the disclosure is non-enabling. To the contrary, references have been furnished to demonstrate, generally, in the

field of protein chemistry one cannot readily ascertain the activity based on structure alone. One cannot readily conclude nor predict that analogs will have the same activity or similar activity to a single peptide with a known activity. Rudinger et al. indicates the difficulty associated with changing even a single amino acid let alone more than one amino acid in the determination of activity. Applicants have stated that one skilled in the art would the critical region of IGFBP has been described in the art and thus one of ordinary skill in the art would be able to alter amino acid residues in the binding protein and/or receptor binding domain. However, it far more complex then just determining the binding ability of the null IGF. First, one of ordinary skill in the needs to determine what modifications are possible, second the binding ability of the possible analogs need to be determined and, third a determination if null IGF displaces native IGF-1 from complexes with binding protein needs to be made, finally that this analog would be effective in-vivo and thus inhibit tumor growth. One of ordinary skill in the art would have to determine the pharmokinetics, such as drug absorption and drug clearance, of the analog before it could be utilized in the inhibition of tumor growth in an individual. This is because the one could not predict, due to the structural changes, that the analog would have the same pharmokinetics as native IGF or another IGF analog. The specification does not provide any guidance in making these determinations. In their response, Applicants even state that the basis for the conclusion is theoretical. "The specification provides a theoretical basis for the importance of two properties, i.e., null IGF displaces native IGF-1 from complexes with binding protein....resulting in reduced IGF-1 activity, which reduces growth of tumors."

Applicants have stated that computer models can be used which are known in the art. However, it is well known in the art that computer modeling cannot sufficiently predict protein

structure nor predict the efficacy of the therapeutic agent. Again attention is directed to Ngo et al. which teach that computer modeling fall short of the task in structure prediction. Further, Berendsen et al. also state that "existing computers cannot sample enough configurations in a reasonable time to come up with the thermodynamically stable native structure; second, we are not sure that the available force field description, which we need to compute the energy of each configuration, are accurate enough to come up with a reliable free energy of conformation." In another article in the Apri 1992 Science, it is disclosed that although computers can be used to design drugs, "for the most part technicians must still screen many, many compounds to find their magic bullets." (see page 441). The article concludes that computer models are not an effective method of determining drug activity. "Even modest gains in the ability to predict drug activity from structural data will be enough to delight some computational biologist. 'Developing drugs is a vague science in which you synthesize a large number of compound." (See page 441). Thus, unlike applicants contention, a determination of the in-vivo efficacy is undue experimentation since more work the simply routine assay are required to determine if an analog would be effective in inhibiting tumor growth.

Although Applicants are not required to provide every species to render a claimed invention enabled, it has been constantly held that lack of working examples or presence of a single example are a factor to be considered in the enablement analysis. A recurring problem is whether a specification that sets forth a single or a limited number of examples can be enabling of broad claims when the subject matter concerns biological materials or reactions, which are generally considered to be unpredictable. For example, In Amgen, Inc. v. Chugai Pharmaceutical Co. LTD., 927 F.2d 1200, 18 USPQ 2d 1016 (Fed. Cir. 1991), the court held a generic claim covering all

DNA sequences that would encode a protein sufficiently duplicative of EPO that it had the property of increasing the production of red blood cells as nonenabling. The court stated:

> "Considering the structural complexity of the EPO gene, the manifold possibilities for change in its structure, with attendant uncertainty as to what utility will be possessed by these analogs, we consider that more is needed concerning identifying the various analogs that are within the scope of the claim, methods for making them, and structural requirements for producing compounds with EPO-like activity. It is not sufficient, having made the gene and a handful of analogs whose activity has not been clearly ascertained, to claim all possible genetic sequences that have EPO-like activity. Under the circumstances, we find no error in the court's conclusion that the generic DNA sequence claims are invalid under Section 112." Id. at 1214.

Here, like in Amgen, Applicants are claiming a generic peptide sequence that covers all variants of IGF-1. The specification does not provide guidance as to what amino acids of the 60 amino acids are not essential amino acids may be substitute, retained or deleted. Unlike Amgen, the specification discloses only one analog that would be representative of the generic claim. Thus, given the unpredictiblity associated with structure changes and the lack of guidance provided in the specification, one would be burdened with undue experimentation to practice the claimed invention.

Rejection is maintained.

5. The reference of Berendsen et al. and April Science Article have been cited to establish the state of the art for computer modeling and rebut Applicants contentions about computer modeling.

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (703) 308-4001. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda , can normally be reached on (703)306-3220. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Anish Gupta 10/28/02

Brenda Brumback

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